IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jens PETERSEN
Title:	**POLYACRYLAMIDE HYDROGEL FOR THE TREATMENT OF INCONTINENCE AND VESICOURETAL REFLUX**
Appl. No.:	09/938,667
Filing Date:	08/27/2001
Examiner:	Blessing M. Fubara
Art Unit:	1618
Confirmation No.	2505

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

(1) I, Robert Lessél, am an expert in polymer chemistry ("the field"). My qualifications as an expert in the field are detailed in a curriculum vitae that is an APPENDIX 2 to this Declaration.

(2) I provide consultation and know-how to Contura S.A. pursuant to an agreement on matters of process polymer chemistry.

(3) I have reviewed the pending claims of the subject application. Additionally, applicant's representative to the PTO has informed me of certain issues that have arisen in the prosecution of the subject application.

(4) Accordingly, with respect to whether the polymerization goes to completion, I understand the Examiner to be of the opinion that the presence of the residual monomer in the product (of the Pavlyk patent) is expected to be minimal if any, thereby rendering the "less than 50 ppm" recitation in claim 9 to be obvious. Thus informed, I understand the examiner to believe that the hydrogel ("the prior-art hydrogel") described in the Pavlyk patent (US 5,798,096) is a "hydrogel" as recited in claim 9 of the subject application.

(5) To illustrate the prior-art hydrogel, the Pavlyk patent presents several "preparation" examples (see columns 4 and 5), each of which states that a mixture of constituents "was filtered through a glass filter and the filtrate was allowed to stand for at least 20 minutes until … hydrogel was formed" (e.g., "Example 1" at column 5, lines 4 – 6). There also is mention of obtaining, for test purposes, "extracts from the novel hydrogel … by soaking … samples thereof for 14 and 30 days at a temperature of 40 deg. C…" (column 7, lines 34 – 36). Neither of these disclosures nor any other passage from the Pavlyk patent implicates washing or soaking in the preparation of the prior-art hydrogel.

(6) The Pavlyk patent describes a hydrogel as suitable in certain terms that are rheological (e.g., in column 3, lines 41 – 53) or toxicological (e.g., in column 7, lines 46 – 66), *inter alia*. In the latter regard, the Pavlyk patent relates testing "in conformity with" a certain Russian "Guidance on toxicological and hygienic examination of polymeric materials …." *circa* 1987, whereby "extracts from the novel hydrogel" were subjected to "drying … at room temperature" and then to HPLC analysis (column 7, lines 34 – 44). According to the Pavlyk patent:

> Acrylamide was not detected by the HPLC in aqueous extracts from the hydrogel prepared by the method [summarized above] to indicate that on the whole … the biocompatible hydrogel of the invention [is] chemically stable.

Column 7, lines 50 – 54 (underscoring added).

(7) It is our understanding of the Pavlyk patent, particularly from column 6, lines 32-33 and column 7, lines 50-54, that monomer content was investigated for purposes of determining the chemically stability of the polymer, rather than determining the degree to which the reaction went to completion or for determination of the residual monomer content. Pavlyk makes no mention of removing residual monomer, but rather is intent on identifying decomposition products of the polymer, namely acrylamide, in order to establish the chemical stability of the polymer.(It should be noted that products of less than 3.5% were judged unstable, although no data was provided with regards to decomposition products.).

(8) In the above context, Table 3 of the Pavlyk patent in fact appears to reveal that the polymer contains leachables. For Test 1 and 2 in the table, the percentage recovery of solid is 94.3 and 94.4wt% (calculation based on starting concentration of 5%). For Test 3 and 4, where the gel has been soaked in water and changed every day before a final determination of solid content,

the percentage recovery of solid content is only 89.4 and 89.5 wt%. A difference of 5 wt% is unaccounted for in the prepared polymer intended for use, compared to the polymer tested for decomposition products.

(9) In this context, it is noted that in column 4, lines 48-58, the prepared polymer intended for use is controlled for a number of features, but is not controlled for residual monomer content

(10) In the aforementioned period, I collaborated with Contura S.A. with respect to developing further the technology described in the Pavlyk patent. In the context of that collaboration I learned that HPLC testing of "extracts from the novel hydrogel," in accordance with the Pavlyk patent, was misleading to the extent of indicting no acrylamide monomer in the prior-art hydrogel. Rather, by virtue of the fact that the acrylamide polymerization reaction proceeds only to between about 94% and 96% completion, the method described in Pavlyk patent leads to a prior-art hydrogel having a residual monomeric content above 50 ppm. When we performed Examples 1-3 of the Pavlyk patent in quadruplicate, we detected a mean amount of residual monomeric acrylamide of 1278 ppm in the product of Example 1, a mean amount of residual monomeric acrylamide of 2646 ppm in the product of Example 2, and a mean amount of residual monomeric acrylamide of 693 ppm in the product of Example 3. Our results do not support the position that the product of the Interfall patent to be a hydrogel of claim 9, nor a product with minimal residual monomer content.

(11) The Pavlyk patent does not recognize the problem of possible residual monomer, describes the preparation of a polymer hydrogel with a high residual monomer content, and provides no guidance useful to solving the problem of residual monomer. In contradistinction, the inventor of the subject application discloses, e.g., in paragraphs [0030] and [0031] of the published version, that a polyacrylamide material of suitable biocompatibility could be prepared via a process that involves an extensive washing. The result of this extensive washing is a substantially lower residual acrylamide monomer content, "less than 50 ppm monomeric units." as determined by a reliable analytical method and as prescribed by the pending claims.

(12) In our work as process chemists, requirements for products are placed upon us for toxicological purposes. It is our understanding that significant toxicological consequences arise from the difference in acrylamide monomer content between less than 50 ppm, as the pending claims require, and a acrylamide content resultant from the method of the Pavlyk

patent, wherein no washing takes place (compare paragraphs 7 and 8 with paragraph 9, *supra*). In particular, the result of the extensive washing taught by the subject application is an improved biocompatibility, relative to the prior-art hydrogel as described by the Pavlyk patent that is the consequence of a reduced acrylamide monomeric content.

(13) I further declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 6th June 2008

By: _____
Robert Lessel, Chempilots a/s
Farum, Denmark

Results

Residual acrylamide in gels prepared according to US 5,798,096:

We have replicated examples 1-3 in US patent 5,798,096 as described.

2x2 samples for analysis were taken from each of the finished gel product from example 1-3 and analysed according to CP standard method for determination of residual acrylamide in polyacrylamide gel i.e. aqueous extraction and determination on each extract by HPLC.

The results are given in table 1 below.

Table 1. Residual acrylamide in polyacrylamide gels prepared according to US 5,798,096

Example	Amount of acrylamide content (ppm) in		Mean value (ppm) for
	sample 1a+b	sample 2a+b	all four determinations
1	1571	1138	1278
	1594	809	
2	5099	382	2646
	2835	2269	
3	553	1040	693
	490	688	

CP reference numbers for more details regarding preparation and analyses: CP144375, CP144377, CP144379, CP20800681 and 2370036.

The results in table 1 clearly show that the gel made according to the examples in US patent 5,798,096 contain an amount of non-reacted acrylamide far above 50ppm.

The results indicate that there are variation between the single values obtained for samples taken out from different spots within the same gel lump. This is quite normal for a bulk product and the variations might in addition reflect that extraction equilibrium has not been fully obtained for the sample with the highest concentration of residual acrylamide in example 2.
The single values in example 2 should therefore be considered as minimum values.

Primary investigator: Robert Lessèl.
Chemptools a/s
Farum, the 27th of November 2007.

APPENDIX 1

APPENDIX 1

Example 1 of US 5,798,096

	amount	moles
Monomer-part		
Water approx in g	558,85	
TEMED in g	0,075	0,0006
Acrylamide in g	20,30	0,2856
Bis-AM in g	0,174	0,0011
	579,40	
AMPS-part		
AMPS in g	0,60	0,0026
Total amount =	580,00	
Dry solid content % =	3,65%	
MR AM/BIS-AM =	253	
MR AM+BIS-AM/TEMED =	444	
MR AM+BIS-AM/AMPS =	109	
MR AMPS/TEMED =	4,07	

Transformed into CP recipe	amount	moles
Monomer-part		
Water in g	518,81	
TEMED 99% in ml	0,097	0,0006
Acrylamide 40%-sol in g	51,82	0,2856
Bis-AM 2%-sol in g	8,70	0,0011
	579,40	
AMPS-part		
AMPS in g	0,60	0,0026
Total amount =	580,00	
Dry solid content % =	3,65%	
MR AM/BIS-AM =	253	
MR AM+BIS-AM/TEMED =	444	
MR AM+BIS-AM/AMPS =	109	
MR AMPS/TEMED =	4,07	

8,7 ml of 2% aq methylene-bis-acrylamide = 0,174g BISAM and 8,526g water
7,5 ml of 1% aq TEMED solution = 0,075g TEMED and 7,425g water
15 ml of 4% aq AMPS solution = 0,600g AMPS and 14,4g water
Calculated amounts introduced into sterile glass vessel (1 ltr) and stirred.
The mixture is filtrated and allowed to stand until the cross-linked hydrogel is formed (at least 20 min).

Example 2 of US 5,798,096

	amount	moles
Monomer-part		
Water approx in g	345,02	
TEMED in g	0,060	0,0005
Acrylamide in g	34,20	0,4811
Bis-AM in g	0,600	0,0039
	379,88	
AMPS-part		
AMPS in g	0,12	0,0005

Total amount = 380,00
Dry solid content % = 9,21%
MR AM/BIS-AM = 124
MR AM+BIS-AM/TEMED = 939
MR AM+BIS-AM/AMPS = 922
MR AMPS/TEMED = 1,02

Transformed into CP recipe	amount
Monomer-part	
Water in g	262,54
TEMED 99% in ml	0,078
Acrylamide 40%-sol in g	87,28
Bis-AM 2%-sol in g	30,00
AMPS-part	
AMPS in g	0,12

Total amount = 380,00
Dry solid content % = 9,20%
MR AM/BIS-AM = 124
MR AM+BIS-AM/TEMED = 939
MR AM+BIS-AM/AMPS = 922
MR AMPS/TEMED = 1,02

60 ml of 1% aq methylene-bis-acrylamide = 0.6 g BISAM and 59,4g water
6 ml of 1% aq TEMED solution =0.06g TEMED and 5,94g water
25 ml of 0,48% aq AMPS solution = 0.12g AMPS and 24,88g water
Calculated amounts introduced into sterile glass vessel (1 ltr) and stirred.
The mixture is filtrated and allowed to stand until the cross-linked hydrogel is formed (at least 20 min).

Example 3 of US 5,798,096

Transformed into CP recipe

	amount	moles		amount	moles
Monomer-part			Monomer-part		
Water approx in g	324,60		Water in g	262,85	
TEMED in g	0,250	0,0022	TEMED 99% in ml	0,325	0,0022
Acrylamide in g	24,00	0,3376	Acrylamide 40%-sol in g	61,25	0,3376
Bis-AM in g	0,500	0,0032	Bis-AM 2%-sol in g	25,00	0,0032
	349,35			349,35	
AMPS-part			AMPS-part		
AMPS in g	0,65	0,0028	AMPS in g		

Total amount = 350,00		Total amount =	
Dry solid content % =	7,26%	Dry solid content % =	
MR AM/BIS-AM =	104	MR AM/BIS-AM =	
MR AM+BIS-AM/TEMED =	158	MR AM+BIS-AM/TEMED =	
MR AM+BIS-AM/AMPS =	120	MR AM+BIS-AM/AMPS =	
MR AMPS/TEMED =	1,32	MR AMPS/TEMED =	

50 ml of 1% aq methylene-bis-acrylamide =0,5 g BISAM and 49,5g water
25 ml of 1% aq TEMED solution = 0.25g TEMED and 24,75g water
50 ml of 1,3% aq AMPS solution = 0,65g AMPS and 49,35g water
Calculated amounts introduced into sterile glass vessel (1 ltr) and stirred.

The mixture is filtrated and allowed to stand until the cross-linked hydrogel is formed (at least 20 min).

APPENDIX 2

CURRICULUM VITAE

Name:	Robert Lessèl.
Nationality:	Danish.
Address:	Bryggerdammen 21, 2605 Brøndby, Denmark.
Telephone:	3675-8830.
Born:	6. august 1963 in Glostrup, Copenhagen.
Personal status:	Married, 3 children age 8, 14 and 17.
Education:	1982: Graduated high school, Statsgymnasiet Schneekloths skole 1988: M. Sc.(Eng.), Chemical Engineer, Technical University of Denmark, specialized in polymer chemistry. Examination work: Modification of polymeric membranes and Phenyl substituted aromatic liquid crystalline polymers. 1989: Patent Examiner at The Danish Patent Office. 1996: Examined as Project Manager, ETM, IHB-Denmark. 2003: Introduction to Management, Right Kjaer & Kjerulf.
Employments:	October 1988 - December 1990 Patent Examiner at The Danish Patent Office within the area "Phosphoric Compounds and polymers". January 1991- ...: Project Manager and Consulting Engineer within polymeric chemistry & processing at Chempilots a/s (previously Wolff & Kaaber A/S). Chempilots work has included: Independent problem-solving, preparation of experimental plans, experiments in the laboratory and at the client, reporting and follow up. Internal/external collaboration with scientific and technical staff including direct

customer contacts with several Danish and International companies, mainly from the Medical Device industry.

Examples of major Projects:

1991: "Development of effective resin composites as substitute for amalgam", performed in association with Dr. Odont E.C.Munksgaard, Dental School, Copenhagen.
The project is supported by the Danish Environmental Protection Agency.

1994-2000: MUP II program: "Stability and strength of the bonds between polymers and the inorganic fillers", in association with the Danish company Nordisk Tråd & Kabel A/S (NKT research center) and two state laboratories at H C Ørsteds institute, University of Copenhagen and Risø, Department of Solid state Physics.

1999-2002: Thor program: " Design of new functional polymer composite Materials"; exploration of the use of supercritical CO_2 as solvent in preparation and modification of polymeric based materials.

Optimization of Bone Cement formulation, Polyurethane foam and Controlled Release system. Processing assignments with regards to Casting of plastic Fresnel screens. Synthesis of Polymer based materials used as conducting/medical skin adhesives and ECG, and development and synthesis/ analysis of polymeric based Hydrogel products for use as colorants for soft contact lenses and soft tissue filler.

Handling of patent applications internally and for customers including elaboration of patent applications, forming strategies and drawing up budgets, correspondence with Danish and foreign patent agents.

Supplementary achievements and references:

Participated regularly in national and international congresses, courses, meetings and workshops since 1988 within the scientific areas of Polymer Chemistry and Technology, Synthesis and processing of Polymer based Hydrogels, Characterization and Analysis of Polymeric based materials and Patent related topics.

Training courses in HPLC, Perkin Elmer.

Trained in ISO9001 and GMP for use in laboratory and production.

Trained in literature searching using STN incl. Chemical Abstract.

Taken classes in Taguchi experimental planning and Statistic with Statgraphic, DIEU.

Teaching experience & publications :

1990: Instructor in Patent examination, The Danish Patent Office.

1991: Internal lecture, Topic: Patents - protection of research and development.

1992: Lecture for leading staff at dnp denmark A/S, topic: Polymerization processes in manufacturing of Fresnel screens.

1995: Invited speaker to a meeting arranged by the DSM, a society under The Society of Danish Engineers, topic: Use of polymeric composite materials instead of amalgam.

2004: Invited speaker at the annually meeting in the Society of Processing in Organic Chemistry, Cheminova: Use of Supercritical CO_2 in Organic Chemistry.

2000: Co-inventor on several patent applications regarding polyacrylamide based hydrogels.

1990: M.H.B. Skovby, R. Lessèl and J. Kops, J.: Thermal

properties of Some Fully Aromatic Thermotropic Liquid Crystal Polyesters Polym. Sci. A. Polym. Chem. Ed., 28, 75 (1990)

1990: Article i Patentdirektoratets personaleblad om "Nordiske Polymerdagar 1990", R. Lessèl, 9/1990.

1992-1998: Munksgaard, EC, Wolff & Kaaber A/S: Erstatningsmaterialer for sølvamalgam, Arbejdsrapport, Miljøstyrelsen 1992, 1994, 1997 og 1998

1996: Artikel i Tandlægebladet: Plastfyldninger i støbeskeen, 100, 1996, s. 190 -191

1997: Interview til Materiale & Muligheder: Ny viden om avanceret plast.

1998: Munksgaard, EC, Wolff & Kaaber A/S: Erstatningsmaterialer for Amalgam til tandfyldninger, Projektrapport, Miljøstyrelsen 1998

1997: Lessèl, R; Elbek, C: Rheological Characterization of highly filled dental restorative composite in the uncured state; Poster at Nordic Polymer Days, Lund.

2000: Egsgaard, H; Batsberg, W; Møllgaard, M; Lessèl, R; Glastrup, J: Mass spectrometry of Polyethylene Glycols; Proceeding and poster at International MS meeting in Barcelona.

Schaumburg, K; Jespersen, H.T; Khokhlov, A; Karthäuser, J; Lessèl, R: Kemi i superkritisk CO_2; dansk kemi, 84, nr. 11, s. 26 – 30.

Memberships:

1990: Member of the Advisory committee on the project "Development of effective resin composites as substitute for amalgam", appointed by the Danish Environmental Protection Agency.

1999-2002: Member of the Steering group FUCOMA in the public financed THOR project " Design of new functional polymer composite materials".

2008- : Member of the board of the Danish Society for Polymer Technology under the Danish Society of Engineers, IDA.